

What is claimed is:

1. A method of determining a chromosomal breakpoint in a subject suffering from multiple myeloma which comprises steps of:
 - (a) obtaining a DNA sample from the subject suffering from multiple myeloma;
 - (b) determining whether there is J and C disjunction in the immunoglobulin heavy chain gene in the obtained DNA sample;
 - (c) obtaining a genomic library having clones which contain genomic DNA fragments from the DNA sample which shows positive J and C disjunction;
 - (d) selecting and isolating clones of the obtained library which show positive hybridization with a probe which is capable of specifically hybridizing with the C but not the J region of the immunoglobulin heavy chain gene;
 - (e) preparing fluorescent probes from the genomic DNA fragments of the isolated clones from step (d);
 - (f) hybridizing said fluorescent probes with metaphase chromosomes; and
 - (g) determining the identity of the chromosomes which are capable of hybridizing to said fluorescent probes, wherein the identification of a chromosome other than chromosome 14 would indicate that the chromosomal breakpoint is between chromosome 14 and the identified chromosome, thereby determining a chromosomal breakpoint in a subject suffering from multiple myeloma.
2. The method of claim 1, wherein step (b) is performed by Southern blotting.

3. The method of claim 1, wherein step (b) is performed by polymerase chain reaction with appropriate probes.
4. The method of claim 1, wherein the genomic library is a phage vector library.
5. The method of claim 4, wherein the genomic DNA fragments are generated by cleaving genomic DNA from cells of the subject with an appropriate restriction enzyme.
6. The method of claim 5, wherein the restriction enzyme is *Bam*HI.
7. The method of claim 5, wherein the restriction enzyme is *Sau*3AI.
8. The method of claim 1, wherein the probe of step (d) is a human IgH J region JH probe.
9. The method of claim 1, wherein the probe of step (d) is a human IgH C μ probe.
10. The method of claim 1, wherein the probe of step (d) is a human IgH Cy2 probe.
11. The method of claim 1, wherein the chromosomal breakpoint identified is a t(6;14)(p25;q32) translocation.
12. The method of claim 1, wherein the chromosomal breakpoint identified is a t(14;15) translocation.

13. A method to identify a gene other than the immunoglobulin gene which is located in chromosome 14, altered by a chromosomal breakpoint detected in a subject suffering from multiple myeloma which comprises steps of:

- a) selecting a probe having a sequence of a chromosome other than chromosome 14, identified at the chromosomal breakpoint detected in a subject suffering from multiple myeloma, wherein said probe is capable of hybridizing to the unique sequence of the gene other than the immunoglobulin gene altered by a chromosomal breakpoint detected in a subject suffering from multiple myeloma;
- b) contacting said probe with mRNA isolated from a cell under conditions permitting formation of a complex between said probe and the mRNA;
- c) isolating the complex resulting from step (b);
- d) determining the sequence of the mRNA in the isolated complex, thereby determining the identity of the gene.

14. The method of claim 13, wherein step (d) comprises steps of:

- i) synthesizing complementary DNA to the mRNA; and
- ii) performing sequence analysis of the complementary DNA to determine the sequence of the mRNA.

15. A gene identified by the method of claim 13.
16. The gene of claim 15 designated *MUM-1*.
17. The gene of claim 15 designated *MUM-2*.
18. The method of claim 13, wherein the gene identified comprises a nucleic acid encoding a MUM protein.
19. The method of claim 18, wherein the MUM protein is MUM-1.
20. The method of claim 18, wherein the MUM protein is MUM-2.
21. An isolated nucleic acid molecule encoding a MUM protein.
22. An isolated nucleic acid molecule of claim 21, wherein the nucleic acid molecule is a DNA molecule.
23. The isolated DNA molecule of claim 21, wherein the DNA molecule is a cDNA molecule.
24. The isolated DNA molecule of claim 21, wherein the DNA molecule is a cDNA molecule having the nucleotide sequence shown in Figure 5B (SEQ. ID NO).
25. The isolated DNA molecule of claim 21, wherein the DNA molecule is genomic DNA molecule.

26. The isolated nucleic acid molecule of claim 21, wherein the nucleic acid molecule is an RNA molecule.
27. An isolated nucleic acid molecule of claim 21, wherein the nucleic acid molecule encodes a human MUM-1 protein.
28. An isolated nucleic acid molecule of claim 21, wherein the nucleic acid molecule encodes a human MUM-2 protein.
29. An isolated nucleic molecule of claim 31, wherein the human MUM-1 protein has substantially the same amino acid sequence as shown in Figure 5B (SEQ. ID NO).
30. An isolated nucleic molecule of claim 31, wherein the human MUM-1 protein has the amino acid sequence as shown in Figure 5B (SEQ. ID NO).
31. An isolated nucleic acid molecule of claim 21 operatively linked to a promoter of RNA transcription.
32. A vector comprising the nucleic acid molecule of claim 21.
33. A vector comprising the nucleic acid molecule of any claim 23.
34. A vector comprising the nucleic acid molecule of claim 25.
35. A vector of claim 36, wherein the vector is a plasmid.
36. The plasmid of claim 35, designated pcMUM1-1.6a (ATCC

Accession No.).

37. The plasmid of claim 35, designated pMUM1-2.4B/N (ATCC
Accession No.).

5

38. The plasmid of claim 35, designated pMUM1-7.7B (ATCC
Accession No.).

10

39. The plasmid of claim 35, designated pcMUM2-8 (ATCC
Accession No.).

40. A host cell comprising the vector of claims 32.

15

41. The host cell of claim 40, wherein the cell is selected
from a group consisting of a bacterial cell, a plant
cell, and insect cell and a mammalian cell.

20

42. A nucleic acid probe comprising a nucleic acid molecule
of at least 15 nucleotides capable of specifically
hybridizing with a unique sequence included within the
sequence of a nucleic acid molecule encoding a MUM
protein.

25

43. A nucleic acid probe comprising a nucleic acid molecule
of at least 15 nucleotides which is complementary to a
sequence of the isolated nucleic acid molecule encoding
a MUM protein.

30

44. The nucleic acid probe of either of claims 42 or 43,
wherein the MUM protein is MUM-1.

45. The nucleic acid probe of either of claim 42 or 43,
wherein the MUM protein is MUM-2.

46. A DNA probe of claim 44 or 45.

47. A RNA probe of claim 44 or 45.

5 48. A genomic DNA probe of claim 44 or 45.

49. A nucleic acid probe of claim 44 or 45 labeled with a detectable marker.

10 50. The nucleic acid probe of claim 49, wherein the detectable marker is selected from the group consisting of a radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.

15 51. A nucleic acid probe of claim 44, wherein the sequence of a nucleic acid molecule encoding a MUM-1 protein is linked to a nucleic acid sequence capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule
20 of human chromosome 14.

25 52. A nucleic acid probe of claim 45, wherein the sequence of a nucleic acid molecule encoding a MUM-2 protein is linked to a nucleic acid sequence capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule of human chromosome 14.

30 53. A nucleic acid probe comprising a nucleic acid molecule of at least 15 nucleotides which is complementary to a sequence of the isolated nucleic acid molecule of claim 21 which is linked to a nucleic acid sequence complementary to a sequence of a nucleic acid molecule of human chromosome 14.

54. The nucleic acid probe of claim 53, wherein the isolated nucleic acid molecule encodes MUM-1.
55. The nucleic acid probe of claim 53, wherein the isolated nucleic acid molecule encodes MUM-2.
56. The nucleic acid probe of claim 54, wherein the sequence of a nucleic acid molecule encoding a MUM-1 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14.
57. The nucleic acid probe of claim 55, wherein the sequence of a nucleic acid molecule encoding a MUM-2 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14.
58. The nucleic acid probe of claim 56, wherein the specific break point comprises a portion of the t(6;14)(p25;q32) translocation.
59. The nucleic acid probe of claim 57, wherein the specific break point comprises a portion of a t(14;15) translocation.
60. The nucleic acid probe of either of claims 58 or 59 labeled with a detectable marker.
61. The nucleic acid probe of claim 60, wherein the detectable marker is selected from the group consisting of a radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.
62. A method for detecting a predisposition to multiple myeloma associated with the expression of a human MUM-1

protein in a sample from a subject which comprises detecting in a sample from the subject a rearrangement of nucleic acid encoding MUM-1 protein.

- 5 63. A method for detecting a predisposition to multiple myeloma associated with the expression of a human MUM-2 protein in a sample from a subject which comprises detecting in a sample from the subject a rearrangement of nucleic acid encoding MUM-2 protein.
- 10 64. The method of claim 62, wherein the rearrangement of nucleic acid encoding MUM-1 protein is detected by contacting the nucleic acid from the sample with a MUM-1 probe under conditions permitting the MUM-1 probe to hybridize with the nucleic acid encoding MUM-1 protein from the sample, thereby detecting the rearrangement of nucleic acid encoding MUM-1 protein in the sample.
- 15 65. The method of claim 63, wherein the rearrangement of nucleic acid encoding MUM-2 protein is detected by contacting the nucleic acid from the sample with a MUM-2 probe under conditions permitting the MUM-2 probe to hybridize with the nucleic acid encoding MUM-2 protein from the sample, thereby detecting the rearrangement of nucleic acid encoding MUM-2 protein in the sample.
- 20 66. The method of claim 64, wherein the MUM-1 probe comprises a nucleic acid molecule of at least 15 nucleotides which is complementary to a sequence of the isolated nucleic acid molecule encoding MUM-1 protein which is linked to a nucleic acid sequence complementary to a sequence of a nucleic acid molecule of human chromosome 14.
- 30 67. The method of claim 65, wherein the MUM-2 probe
- 35

comprises a nucleic acid molecule of at least 15 nucleotides which is complementary to a sequence of the isolated nucleic acid molecule encoding MUM-2 protein which is linked to a nucleic acid sequence complementary to a sequence of a nucleic acid molecule of human chromosome 15.

68. The method of claim 66, wherein the nucleic acid molecule of at least 15 nucleotides which is complementary to a sequence of the isolated nucleic acid molecule encoding MUM-1 protein is linked at a specific break point to a nucleic acid sequence complementary to a sequence of a nucleic acid molecule of human chromosome 14.

69. The method of claim 67, wherein the nucleic acid molecule of at least 15 nucleotides which is complementary to a sequence of the isolated nucleic acid molecule encoding MUM-2 protein is linked at a specific break point to a nucleic acid sequence complementary to a sequence of a nucleic acid molecule of human chromosome 15.

70. The method of claim 68, wherein the specific break point comprises a portion of the t(6;14)(p25;q32) translocation.

71. The method of claim 69, wherein the specific break point comprises a portion of a t(14;15) translocation.

72. The method of claim 62, which comprises:

- a. obtaining DNA from the sample of the subject suffering from multiple myeloma;

- b. performing a restriction digest of the DNA with a panel of restriction enzymes;
- c. separating the resulting DNA fragments by size fractionation;
- d. contacting the resulting DNA fragments with a nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-1 protein, wherein the sequence of a nucleic acid molecule encoding a MUM-1 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14 and labeled with a detectable marker;
- e. detecting labeled bands which have hybridized to the nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-1 protein, wherein the sequence of a nucleic acid molecule encoding a MUM-1 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14 to create a unique band pattern specific to the DNA of subjects suffering from multiple myeloma;
- f. preparing DNA obtained from a sample of a subject for diagnosis by steps (a-e); and
- g. comparing the detected band pattern specific to the DNA obtained from a sample of

subjects suffering from multiple myeloma from step (e) and the DNA obtained from a sample of the subject for diagnosis from step (f) to determine whether the patterns are the same or different and to diagnose thereby predisposition to multiple myeloma if the patterns are the same.

73. The method of claim 63, which comprises:

- a. obtaining DNA from the sample of the subject suffering from multiple myeloma;
- b. performing a restriction digest of the DNA with a panel of restriction enzymes;
- c. separating the resulting DNA fragments by size fractionation;
- d. contacting the resulting DNA fragments with a nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-2 protein, wherein the sequence of a nucleic acid molecule encoding a MUM-2 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14 and labeled with a detectable marker;
- e. detecting labeled bands which have hybridized to the nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-2

protein, wherein the sequence of a nucleic acid molecule encoding a MUM-2 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14 to create a unique band pattern specific to the DNA of subjects suffering from multiple myeloma;

f. preparing DNA obtained from a sample of a subject for diagnosis by steps (a-e); and

g. comparing the detected band pattern specific to the DNA obtained from a sample of subjects suffering from multiple myeloma from step (e) and the DNA obtained from a sample of the subject for diagnosis from step (f) to determine whether the patterns are the same or different and to diagnose thereby predisposition to multiple myeloma if the patterns are the same.

74. The method of claim 72 or 73, wherein the size fractionation in step (c) is effected by a polyacrylamide or agarose gel.

75. The method of claim 72 or 73, wherein the detectable marker is radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.

76. A method of claim 62 which comprises:

a. obtaining RNA from the sample of the subject suffering from multiple myeloma;

- b. separating the RNA sample by size fractionation;
- 5 c. contacting the resulting RNA species with a nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-1 protein, wherein the sequence of a nucleic acid molecule encoding a MUM-1 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 14 and labeled with a detectable marker;
- 10
- 15 d. detecting labeled bands which have hybridized to the RNA species to create a unique band pattern specific to the RNA of subjects suffering from multiple myeloma;
- 20 f. preparing RNA obtained from a sample of a subject for diagnosis by steps (a-d); and
- 25 g. comparing the detected band pattern specific to the RNA obtained from a sample of subjects suffering from multiple myeloma from step (d) and the RNA obtained from a sample of the subject for diagnosis from step (f) to determine whether the patterns are the same or different and to diagnose thereby predisposition to multiple myeloma if the patterns are the same.
- 30

77. A method of claim 63 which comprises:

- 35 a. obtaining RNA from the sample of the subject

suffering from multiple myeloma;

b. separating the RNA sample by size fractionation;

c. contacting the resulting RNA species with a nucleic acid probe capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule encoding a human MUM-2 protein, wherein the sequence of a nucleic acid molecule encoding a MUM-2 protein is linked at a specific break point to a specified nucleic acid sequence of human chromosome 15 and labeled with a detectable marker;

d. detecting labeled bands which have hybridized to the RNA species to create a unique band pattern specific to the RNA of subjects suffering from multiple myeloma;

f. preparing RNA obtained from a sample of a subject for diagnosis by steps (a-d); and

g. comparing the detected band pattern specific to the RNA obtained from a sample of subjects suffering from multiple myeloma from step (d) and the RNA obtained from a sample of the subject for diagnosis from step (f) to determine whether the patterns are the same or different and to diagnose thereby predisposition to multiple myeloma if the patterns are the same.

78. The method of claim 76 or 77, wherein the size

fractionation in step (c) is effected by a polyacrylamide or agarose gel.

5 79. The method of claim 76 or 77, wherein the detectable marker is radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.

10 80. The method of either of claim 72 or 76, wherein multiple myeloma associated with the expression of a specific human MUM-1 is diagnosed.

15 81. The method of either of claim 73 or 77, wherein multiple myeloma associated with the expression of a specific human MUM-2 is diagnosed.

20 82. An antisense oligonucleotide having a sequence capable of specifically hybridizing to an mRNA molecule encoding a human MUM-1 protein so as to prevent overexpression of the mRNA molecule.

25 83. An antisense oligonucleotide having a sequence capable of specifically hybridizing to an mRNA molecule encoding a human MUM-2 protein so as to prevent overexpression of the mRNA molecule.

30 84. An antisense oligonucleotide having a sequence capable of specifically hybridizing to the cDNA molecule of claim 23.

85. An antisense oligonucleotide having a sequence capable of specifically hybridizing to the genomic DNA molecule of claim 29.

86. An antisense oligonucleotide having a sequence capable

5

88. A purified ~~MUM~~ protein, wherein the MUM protein is MUM-1 protein.

89. A purified human MUM-1 protein of claim 88.

90. An antibody directed to a purified MUM-1 protein.

91. An antibody capable of specifically recognizing MUM-1 protein.

92. An antibody of claim 91, wherein the MUM-1 protein is a human MUM-1 protein.

93. A purified MUM protein, wherein the MUM protein is MUM-2 protein.

94. A purified human MUM-2 protein of claim 93.

95. An antibody directed to a purified MUM-2 protein.

96. An antibody capable of specifically recognizing a MUM-2 protein.

97. An antibody of claim 96, wherein the MUM-2 protein is a human MUM-2 protein.

98. An monoclonal antibody of ~~any one of claims 90, 91 and~~
92.

Sub A2

[illegible]

10

15

20

25

30

Sub A3

99. An monoclonal antibody of any one of claims 95, 96, and 97.

5 100. A pharmaceutical composition comprising an amount of the oligonucleotide of any one of claims 82, 84, 85 and 81 effective to prevent overexpression of a human MUM-1 protein and a pharmaceutically acceptable carrier capable of passing through a cell membrane.

10 101. A pharmaceutical composition comprising an amount of the oligonucleotide of any one of claims 83, 84, 85 and 81 effective to prevent overexpression of a human MUM-2 protein and a pharmaceutically acceptable carrier capable of passing through a cell membrane.

15

add A~~4~~